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The Association of Aphasia and Right-sided Motor Impairment in Corticobasal Syndrome

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Abstract

Background: Corticobasal syndrome is defined clinically on the basis of symptoms and findings related to dysfunction of the cerebral cortex and the basal ganglia. Usually, marked asymmetry of motor findings is observed. Although aphasia has now been recognised as a frequent feature of corticobasal syndrome, it remains unclear whether it is usually associated with right-sided motor symptoms, pointing to the involvement of the left hemisphere. Hence, we set out to examine the relationship between the presence of language symptoms and the side affected by extrapyramidal symptoms.
Method: We analysed the electronic care records of patients seen in the years 2003-2013 in the Neurology Department of the University Hospital of Munich. The diagnosis of corticobasal syndrome was discussed in ninety-two individuals. Of those, 38 cases fulfilled diagnostic criteria for corticobasal syndrome.
Results: Aphasia correlated highly with a predominant right-sided movement disorder ($p = 0.002$). In contrast, it was less common in patients with left-sided motor presentation. Dysarthria did not show a preferential correlation ($p = 0.25$).
Conclusions: Our analysis suggests a characteristic presentation of corticobasal syndrome in which motor dysfunction of the right side of the body is associated with aphasia.

Keywords

Corticobasal syndrome; corticobasal degeneration; dementia; Parkinsonism; aphasia; dysarthria

Introduction

One of the most pervasive features of corticobasal syndrome (CBS) is the asymmetrical nature of its presentation. It has been mentioned in the first descriptions of the disease [1] and forms part of most diagnostic criteria [2-3]. It is one of the important features distinguishing it from progressive supranuclear palsy (PSP): a syndrome to which it is closely related clinically as well as pathologically [4].

Asymmetry of findings is not only found on clinical presentation, but can also be seen on neuroimaging such as positron emission tomography (PET) and magnetic resonance imaging (MRI). Typically, the asymmetry of the neurodegenerative process, as judged by cortical glucose metabolism and cortical atrophy, is more pronounced in the hemisphere contralateral to the movement disorder [5]. Lateralized brain atrophy is used to differentiate CBS from other tauopathies [5].

CBS has been conceptualized on the basis of symptoms and findings thought to be related to dysfunction of the cerebral cortex and the basal ganglia. Typically, marked asymmetrical rigidity and apraxia or both are observed. The affected limb can display dystonia, cortical sensory loss, focal myoclonus and the alien or anarchic limb phenomenon [6]. These core clinical features are reflected in the diagnostic criteria proposed by different groups. Before the advent of the new diagnostic consensus criteria (discussed below), the most widely established diagnostic criteria were the Toronto [7], Mayo [6] and Cambridge criteria [8]. The latter two include cognitive impairment. Higher cortical function impairment has frequently been described in the course of CBS [6-10]. The issue of laterality is of particular interest given the recent reinterpretation of CBS by Armstrong as a cognitive disorder with symptoms such as general cognitive impairment, behavioural changes, apraxia, aphasia amongst others as well as motor disorder [3]. The Armstrong revision of the diagnosis of CBS distinguishes clinical research criteria for *probable* CBS and broader criteria for *possible* CBS [3]. However, a recent validation of the Armstrong criteria showed that the recognized clinical phenotypes of CBS are widened, but the specificity of the diagnosis CBS was not sufficiently increased [11].

In terms of pathology, CBS has been associated with different aetiologies. In the majority of clinically diagnosed cases the distinct tauopathy of corticobasal degeneration (CBD) with astroglial inclusions in the form of astrocytic plaques is identified as the underlying histopathological correlate [12]. However, other tauopathies such as PSP, frontotemporal lobar degeneration with tau pathology (FTLD-tau) or Alzheimer's disease (AD) may also present as CBS [13]. Asymmetrical presentation seems to be a common feature of CBS regardless of the underlying pathology [9]. In this context, both motor and cognitive symptoms would be expected to show clear lateralization: contralateral pathology in case of motor symptoms, left-hemispheric pathology in case of aphasia [14]. Accordingly, we would expect an association of right-sided motor symptoms and the presence of aphasia.

No correlation between neuropsychological findings and the hemisphere affected has been shown on the basis of lateralization of the motor abnormality [15]. The only cortical signs that frequently show asymmetry seem to be apraxia and cortical sensory loss [6-8]. This is surprising as it is obvious that "anatomy dictates the dementia phenotype" [16]. As aphasia is caused by left hemisphere dysfunction in most cases, language dysfunction in CBS should be a clearly lateralizing cortical sign [17]. Therefore we set out to correlate the presence of language findings to the side affected by motor symptoms.

Methods

An automated search using the German terms corresponding to "corticobasal degeneration"; "corticobasal degeneration syndrome" or the abbreviations "CBD" or "CBS" as well as the ICD-10 diagnosis code G31.0 was performed on the electronic documentation of the patients seen in the years 2003-2013 in the Neurology Department of the University of Munich. Patients were seen in the outpatient clinic of our movement disorders center and our dementia clinic as well as in the joint inpatient clinic. Electronic documentation was written by experienced residents based on the clinical assessment of the patients and double-checked by an attending with at least a decade of experience in clinical neurology. The principles outlined in the "Declaration of Helsinki" were followed. Ninety-two individual cases were found in whom the clinical diagnosis of CBS was discussed. Clinical documentation was reviewed and evaluated for the course of disease and for detailed description of neurological signs and symptoms. Only cases with complete documentation were reviewed, leading to the exclusion of twenty-four cases which were incompletely documented. The remaining 67 cases were evaluated using Mayo [6] and Cambridge criteria [8] as well as the criteria for CBS recently revised by Armstrong and colleagues [3]. Thirty-eight cases fulfilled at least one of these criteria. Thirty-eight cases fulfilled at least one of these criteria. These cases were reviewed for the hemisphere affected and the presence or absence of speech and language disturbances (aphasia, dysarthria or both). In some records aphasia was described in detail, while in others it was just noted as a present symptom. Hence, if we talk about "aphasia" in this manuscript we refer to cortical language disturbances which include different types of aphasia and may also include aphemia. Independent, of such sub-classification, aphasia is caused by pathology in the cortex of the left hemisphere. Likewise, sub-classifications of dysarthria were not present in all documentations and therefore left out. Hence by the term dysarthria is referring to a speech disturbance of sub-cortical origin which may include origin in the white matter, the basal ganglia, or the cerebellum. Independent of the origin, dysarthria cannot be considered a lateralizing symptom.

Statistical analysis of correlation between aphasia or dysarthria and left hemisphere involvement was performed by two-sided Fisher´s exact test using the respective algorithm of GraphPad Prism version 5.02 (GraphPad software, La Jolla, CA, USA). Statistical analysis of demographical data was performed with the help of Student's t-test.

Results

All cases showed an insidious onset and a progressive disease course. All have received imaging to exclude other identifiable causes such as neoplasia or infarction. No family history of neurodegenerative movement disorder was documented and only one case had a positive family history of dementia. None of the patients showed a marked or sustained effect of levodopa treatment. Evaluation with Mayo [6], Cambridge [8] and Armstrong [3] criteria revealed that 36 out of 68 cases fulfilled all three sets of diagnostic criteria. One patient did fulfil only two of the three sets of criteria. Another patient fulfilled only Cambridge criteria. After extensive discussion, we decided to include both cases that did not fulfil all sets of criteria (see table). Thirty-seven patients fulfilled criteria for *possible* CBS according to the recently revised criteria [3]. Interestingly, only two of these well characterized patients fulfilled the more restrictive criteria of *probable* CBS according to the Armstrong criteria [3] (see table).

The epidemiology of the patient population studied was in line with data reported previously [18]. Eighteen out of the total of 38 patients were female. Mean age at presentation was 67.5 years (standard deviation (SD) 9.7; range 42-87). Mean disease duration prior to presentation

was 23.9 months (SD 16.4; range 2-72). Male and female patients did not differ with regard to age at presentation or to disease duration (mean age female patients alone: 67.1 ±10.0 years; disease duration 24.4 ±16.5 months).

In general, disturbances of speech and language were frequent in the patient population, similar to previous publications about CBS [19]. Interestingly, only two of the 16 patients with aphasia had a movement disorder with predominant involvement of the left side of their body. In all of the 14 patients with aphasia and right sided movement disorder, atrophy and/or hypometabolism were lateralized to the left hemisphere. One of the two patients with aphasia and left sided movement disorder showed predominant atrophy of the left hemisphere (patient 16; see table). In this patient, metabolism was impaired bilaterally, with a more pronounced hypometabolism of the right hemisphere. In the remaining patient with aphasia (patient 18; see table), metabolism was impaired bilaterally, with a more pronounced hypometabolism of the right hemisphere and an atrophy in the right hemisphere. Hence, all patients with aphasia had signs of left hemispherical involvement on neuroimaging. In total, 21 patients presented with right sided movement disorder. Only seven of these patients (33 %) did not show aphasia. In contrast, a total of 17 patients showed a predominant movement disorder on the left side. Only two (12 %) of these patients showed aphasia. These two patients showed involvement of the left hemisphere on neuroimaging (see above). None of the patients without aphasia showed atrophy or hypometabolism predominant in the left cerebral hemisphere. Fisher´s exact test revealed that in our patient population aphasia correlated highly with a predominantly right-sided movement disorder ($p = 0.002$). The relative risk for patients with right-sided movement disorder to present with aphasia compared to patients with left-sided movement disorder is 5.33 (95% confidence interval 1.41 to 20.20). The sensitivity of aphasia to predict left hemisphere involvement as judged by presence of right-sided movement disorder in our CBS sample is 0.88 (95% confidence interval 0.62 to 0.98). Specificity is 0.67 (95% confidence interval 0.43 to 0.85). Nine of the 38 patients (24%) had dysarthria. Seven of the patients had left-sided movement disorder and two had right-sided movement disorder. Statistical testing did not show an association of dysarthria to one lateralization of the movement disorder ($p = 0.25$).

Unfortunately, neuropathology data in our cohort are too scarce to draw conclusions. Only two patients had *post mortem* examination, however, these cases fit with previously published data which suggest that in cases of left hemispherical disease non-fluent language disturbance ante mortem is suggestive for classical CBD pathology [9]. Patient 21 presenting with a severe movement disorder, cortical sensory loss and right arm apraxia showed atrophy of the left hemisphere and aphasia. This patient had typical CBD histopathology. Interestingly, he did not fulfil criteria for *probable* CBS according to Armstrong [3]. Patient 13 presenting with rigidity and apraxia of the left hand and hypometabolism of the right hemisphere did not show CBD pathology but displayed abundant p62 pathology and some Alzheimer's changes.

Discussion

Asymmetry and laterality belong to the most puzzling aspects of neurodegenerative diseases. Some types of neurodegenerative conditions are relatively symmetrical (e.g. PSP), others are characterised by a pronounced asymmetry (e.g. CBS or Parkinson´s disease). Our observations suggest a presentation of CBS in which movement disorder of the right side of the body is associated with aphasia and atrophy/hypometabolism of the left hemisphere. ~~We would like to propose the term "left hemispherical presentation of CBDS" for this asymmetrical complex of symptoms.~~ Corticobasal syndrome, with its asymmetrical presentation and the combination of motor and cognitive features offers a particularly good model to study laterality and we hope that our observations will lead to larger, systematic and

prospective studies of this phenomenon in CBS. In the left hemispherical presentation of CBS, aphasia appears at the onset of the movement disorder or evolves within 48 months. It is surprising that this association of findings (aphasia and right-sided motor impairment) has not been mentioned before [10,19]. One study looking at this issue did not find this typical phenotype [15].

Current diagnostic criteria for CBS do not include correlation of the side affected by the movement disorder with typical neuropsychological symptoms of the contra-lateral hemisphere [6-8]. Our data suggest that the diagnostic accuracy could be increased by focusing on higher cortical functions [3,5,9,10,20]. Future studies are needed to study if it is possible to predict CBD pathology more precisely in CBS patients with matching of aphasia and right sided motor phenotype.

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